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## The areca nut chewing habit and oral squamous cell carcinoma in South African Indians

### A retrospective study

C. W. VAN WYK, I. STANDER, A. PADAYACHEE, A. F. GROBLER-RABIE

**Abstract** A retrospective study (1983 - 1989) of oral squamous carcinomas and concomitant oral habits was undertaken in South African Indians from Natal. Information came from hospital records and interviews with patients, families and friends. There were 143 oral squamous carcinomas; these occurred in a ratio of 1:1,6 for men and women respectively. Squamous carcinomas of the cheek (buccal mucosa, alveolar sulcus and gingiva) occurred most frequently, especially in women (57/89 - 64%), while in men tongue cancer predominated (22/54 - 41%). Ninety-three per cent of women (83/87) and 17% of men (9/54) habitually chewed the areca nut. Thirty-nine of 57 women (68%) with cheek cancer and 21/25 (84%) with tongue cancer only chewed the nut (no tobacco, snuff or smoking). Analyses confirmed an association between nut chewing and cheek cancer. The odds ratio (OR) for oral cancer in women 25 years and older who only chewed the nut was 43,9 and the attributable risk (AR) 0,89 (89%). With tobacco the OR increases to 47,42 and the AR to 0,91 (91%). The data showed that the areca nut habit with or without tobacco use is important in the development of oral squamous carcinoma. Elimination of this habit can reduce the risk in these women substantially (89 - 91%) if all other factors remain the same.

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The areca nut (popularly but incorrectly known as the betel nut) comes from the palm *Areca catechu*. The areca nut-chewing habit involves the

chewing of pieces or slices of the nut (baked, boiled or raw), chewing of the nut and the betel quid alternatively or chewing of the betel quid only. The betel quid is a package of fresh betel leaf (vine *Piper betle*), the under-surface of which is smeared with lime, that contains pieces of the nut and sometimes catechu (an extraction from the tree *Acacia catechu*) and tobacco or snuff. Many other condiments, sweetening and flavouring agents may be added, depending on taste and custom.<sup>1</sup>

Uncertainty exists as to whether chewing of the nut or quid without the addition of tobacco can lead to oral squamous carcinoma;<sup>2</sup> the main reason for this is that there is insufficient evidence.<sup>3</sup> The consensus of opinion is that there is sufficient evidence that the habit of chewing betel quid containing tobacco is carcinogenic to humans,<sup>3</sup> and studies concluded that it is unlikely that areca nut chewing without tobacco can cause cancer.<sup>4,5</sup>

On the other hand, epidemiological evidence from New Guinea,<sup>6,7</sup> Pakistan<sup>8</sup> and Malaysia<sup>9</sup> indicates that areca nut chewing without tobacco in the quid increases the risk of oral squamous carcinoma. Some controversy surrounds these reports, because information is not always clear about smoking habits and the inclusion of tobacco or snuff in the quid. Another question is whether there is an indirect association between areca nut chewing and squamous carcinoma of the mouth. The habit is associated with submucous fibrosis, which is an insidious chronic oral condition affecting the soft tissues of the mouth and oropharynx. Histologically it is characterised by a deposition of dense connective tissue in these structures. Clinically it is diagnosed by the presence of dense fibrous bands in the cheeks, soft palate, fauces, lips and floor of the mouth. This excessive formation of connective tissue eventually causes permanent trismus. The condition is also regarded as a premalignant condition and it is possible that another carcinogen or irritant may be the initiator of the cancer.

To determine the prevalence of the chewing habit and submucous fibrosis and to analyse the habits related to the disease, a random survey stratified for age and sex was recently undertaken among the Indians of Natal.<sup>1,10,11</sup> Nine cases of oral squamous carcinoma and 1 of upper oesophageal carcinoma were encountered in 129 subjects suffering from submucous fibrosis. All were in the habit of chewing areca nuts but 9 had never smoked or used tobacco in any form. Eight of the 9 oral cancers were situated in the cheeks.

Oral and Dental Research Unit, University of Stellenbosch

C. W. VAN WYK, PH.D., F.D.S. R.C.S., B.CH.D.

A. PADAYACHEE, M.CH.D., B.D.S.

Institute for Biostatistics and Centre for Molecular and Cellular Biology, South African Medical Research Council, Parowvallei, CP

I. STANDER, B.SC. HONS, M.SC.

A. F. GROBLER-RABIE, B.SC. HONS, M.SC.

Experimental work on the carcinogenic potential of the areca nut indirectly supports the epidemiological findings. Evidence exists that the nut itself, aqueous extracts thereof and specific constituents in the nut can be mutagenic and carcinogenic.<sup>12-16</sup>

In view of the controversy about the epidemiological findings with regard to the chewing of areca nuts and oral cancer, the experimental findings and the data collected in Natal,<sup>1,10,11</sup> a retrospective survey of oral squamous carcinoma cases and the associated oral habits of South African Indians was undertaken, and the odds ratio (OR) and attributable risk (AR) for the areca chewing habit determined.

### Subjects and methods

The investigation was undertaken in Natal because: (i) more than 75% of the approximately 1 million South African Indians reside there; (ii) the Natal census figures for 1980, 1985 and 1989 are available for this ethnic group;<sup>17</sup> (iii) treatment of all cancer cases in this province is centralised in a single oncology unit which makes it possible to calculate incidence rates; and (iv) the data that are available about the areca nut habit and submucous fibrosis in the same ethnic group in Natal<sup>1,10,11</sup> can be used for calculation of the OR and AR for areca nut chewing.

All hospital information on patients with oral cancers for the period 1983 - 1989 was recorded; this included age, gender, place of residence, date of diagnosis of malignancy, site of the malignancy, the pathology reports for histological diagnosis and often facts about either special habits or the presence/absence of submucous fibrosis.

To obtain information about the oral habits of the patients with squamous carcinomas, we interviewed patients, families and friends.

The squamous carcinomas were classified according to the *International Classification of Diseases* (ICD 140, 141, 143 - 146).<sup>18</sup> From the census figures it was possible to calculate the annual population figures in Natal for both sexes from 1983 to 1989. This enabled us to determine the average annual incidence and the world standardised rates according to the International Agency for Research on Cancer (IARC).<sup>19</sup> To compare variables with regard to patients and the squamous carcinomas of the different oral sites, the malignancies were classified into 3 groups; those of the tongue (ICD 141), the cheek, including buccal mucosa and gum (ICD 143; 145,0), and cancers of the floor of the mouth, palate and oropharynx (ICD 144; 145,1, 145,8; 146,0). This grouping allowed sufficient numbers for comparison and ruled out the artificial division of tumours of the soft palate and oropharynx, and tumours recorded as originating in the cheek, buccal, gingival, gingival sulcus and alveolar mucosae.

The chi-square test was used to assess a possible association between tobacco use and areca nut chewing and the occurrence of carcinomas of the tongue, cheek and mouth. To determine the OR and the AR,<sup>20</sup> we used 'non-cases' from the same ethnic group as controls; these were seen in 1983 in Natal during a randomised house-to-house survey. The survey, which included subjects of both sexes, was stratified for age and sex. The subjects were divided into the age groups 10 - 14, 15 - 24, 25 - 34, 35 - 44, 45 - 54, 55 - 64 and 65+ years; 147 persons of each sex were seen in each age group. The examination took note of personal details, and comprised a history and a clinical examination of the mouth under natural light.<sup>1,10,11</sup> Given the differences between the sexes with regard to areca nut chewing and smoking habits and the rarity of the chewing habit among men, we calculated the OR and AR

only for women. The women were matched for age, and the effect of areca nut chewing with concomitant tobacco use was compared with areca nut chewing without tobacco use.

### Results

There were 150 patients of Indian extraction with oral cancer, 95 women and 55 men, a ratio of 1,7:1. One hundred and forty-three had squamous cell carcinomas (89 women and 54 men, ratio 1,6:1), and 7 were cancers of salivary gland origin. Of the latter, 6 occurred in women (4 adenoid cystic, 1 muco-epidermoid and 1 acinic cell carcinoma) and 1 in a man (an adenoid cystic carcinoma). The mean age of the women was  $55,2 \pm 10$  years (range 34 - 78 years) and of the men  $56,4 \pm 8,8$  years (range 38 - 75 years).

**Anatomical distribution of oral squamous carcinomas** (Table I). Of the 143 squamous carcinomas 126 occurred on one surface, while the remaining 17 involved more surfaces. In the latter instance the surface most extensively involved was regarded as the primary site of the tumour. Cheek carcinomas were noticeably more common in women, while oropharyngeal and tongue carcinomas were more common in men.

TABLE I.  
Anatomical distribution of intra-oral squamous carcinomas

	Women		Men	
	No.	%	No.	%
Lip (ICD 140)	0		0	
Tongue (ICD 141)	25	28	22	41
Gum (ICD 143)	6	7	0	
Floor of mouth (ICD 144)	3	3	3	6
Buccal mucosa (ICD 145,0)	51	57	11	20
Palate (ICD 145,1, 145,8)	1	1	4	7
Oropharynx (ICD 146,0)	3	3	14	26
Total	89		54	

**The crude and world standardised average annual incidence rates** (Table II). In women the incidence rate for squamous carcinomas of the mouth (ICD 143 - 5) was not only higher than the rates for the other oral sites but also for the oral sites in men. This high figure was due to the comparatively large number of cheek carcinomas (ICD 143; 145,0).

TABLE II.  
Crude and world standardised average annual incidence rates of intra-oral squamous carcinomas (/100 000) (1983 - 1989)

	Women		Men	
	All ages	ASR world	All ages	ASR world
Tongue (ICD 141)	1,0	1,2	0,9	1,6
Mouth (ICD 143 - 5)	2,4	3,5	0,8	1,0
Cheek (buccal mucosa & gum, ICD 143; 145,0)	2,3	3,3	0,5	0,6
Oropharynx (ICD 146,0)	0,1	0,3	0,6	1,2

All ages = crude rate; ASR world = world-standardised rate.

**Histological differentiation of squamous carcinomas** (Table III). The pathology reports, which included full histological descriptions of the tumours, were available in all cases. The majority of carcinomas were well differentiated (62%). These included 5 verru-

cous carcinomas, 2 in men and 3 in women. Four arose in the buccal mucosa and 1 on the gingiva. Snuff dipping was verified in 2 patients.

**Submucous fibrosis.** Thirty-six women were examined for submucous fibrosis on admission to hospital. Of the 19 in whom the disease was diagnosed, all were areca nut chewers, 13 had carcinomas of the cheek, 5 of the tongue and 1 of the mouth floor. Eleven of the 17 without submucous fibrosis were also chewers. No reliable information about submucous fibrosis was available for the remaining patients.

**Information about oral habits.** Information about oral habits was obtained from 75 patients, from families and friends in 42 instances; in 26 cases the hospital records were the only source of information.

The occurrence of habits in relation to the three groups of oral carcinomas are presented in Table IV. (Note that the figures shown are not mutually exclusive.) The most popular habit was areca nut chewing (64%), followed by smoking (37%) and snuff dipping (16%). Forty-five per cent chewed areca nuts without using tobacco in any form. Women preferred chewing areca nuts (93%) and men smoking (87%). There was no significant difference between the information received directly from patients and that given by proxy.

Of women who chewed areca nuts, the majority (53%) preferred only the nut, 13% the betel quid, while 34% liked both. Thirty-six per cent preferred the baked nut, 20% the boiled nut and 3% more than one type. Information about the rest (41%) was unreliable or unavailable. This was the case where details were obtained by proxy, and informants were unable to dis-

tinguish between the boiled or baked nut, which can have a similar appearance when in pieces or slices. On the other hand there was no uncertainty from this source about the use of tobacco, snuff dipping or smoking.

The following variables were cross-tabulated for evaluation of an association between oral carcinomas and habits: the occurrence of tongue carcinomas (ICD 141); cheek carcinomas (ICD 143; 145,0) and cancers of the rest of the mouth (ICD 144; 145,1; 145,8; 146,0) and the number of subjects who used tobacco, who practised the areca nut habit and who practised both habits (Table V). The 2 subjects who did not practise a habit and the 7 for whom information was not complete were not included. The cross-tabulation resulted in 9 cells. A strong association was found between the site of the cancer and the habit ( $P < 0,0005$ ). By comparing the contribution of each cell in the cross-tabulation to the total Pearson chi-square, one could determine in which of them the observed cases differed from the expected number of cases. Thus, subjects who used tobacco had more cancers other than cheek and tongue and fewer cheek cancers than expected and subjects who chewed the nut had fewer cancers other than cheek and tongue and more cheek cancers than expected. The above 4 cells contributed 88% to the total chi-square value (Table V).

We were unable to demonstrate an association between snuff dipping and cheek carcinoma as 13 of the 15 (87%) snuff dippers with cheek cancers practised additional habits and 43 (63%) of the subjects with cheek cancers did not use snuff. The majority of sub-

**TABLE III.**  
**Histological differentiation of squamous carcinomas**

	Women				Men			
	WD	MD	PD	Total	WD	MD	PD	Total
Tongue (ICD 141)	18	6	1	25	12	8	2	22
Gum (ICD 143)	4	1	0	6	0	0	0	
	1*							
Floor of mouth (ICD 144)	2	1	0	3	1	1	1	3
Buccal mucosa (ICD 145,0)	40	8	1	51	5	3	1	11
	2*				2*			
Palate (ICD 145,1, 145,8)	1	0	0	1	2	2	0	4
Oropharynx (ICD 146,0)	0	1	2	3	1	7	6	14
Total	68 (76%)	17 (19%)	4 (5%)	89	23 (43%)	21 (39%)	10 (19%)	54

\*Verrucous carcinomas.  
WD = well-differentiated; MD = moderately differentiated; PD = poorly differentiated.

**TABLE IV.**  
**Occurrence of oral habits in relation to the oral cancers**

	Tongue (ICD 141)		Cheek and gum (ICD 145,0, 143)				Palate, floor, oropharynx (ICD 144, 145,1, 145,8, 146,0)				Total			
	Women (25)		Women (57)		Men (11)		Women (7)		Men (21)		Women (89)		Men (54)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Tobacco habit	3	12	18	32	17	30	9	13	2	10	22	25	47	87
Smoking	0		18	32	5	9	9	13	1	5	6	7	47	87
Snuff	3	12	3	5	14	25	1	14	1	5	18	20	5	9
Cut tobacco	2	8	0		0		0		0		2	2	0	
Areca nut habit	24	96	3	5	55	97	5	71	4	19	83	93	9	17
Areca nut	15	60	2	3	26	46	5	71	3	14	44	49	7	13
Quid	1	4	1	2	10	18	0		0		11	12	1	2
Both	8	32	0		19	33	0		1	5	28	31	1	2
Areca nut habit without tobacco	21	84	1	2	39	68	2	28	2	10	62	70	3	6
Information incomplete	1	4	3	5	1	2	0		2	10	4	4	3	6